Effect of Systemic Hydrocortisone on Brain Abnormalities and Regional Brain Volumes in Ventilator-dependent Infants Born Preterm: Substudy of the SToP-BPD Study

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Objective To evaluate whether a high cumulative dose of systemic hydrocortisone affects brain development compared with placebo when initiated between 7 and 14 days after birth in ventilated infants born preterm.

Study design A double-blind, placebo-controlled, randomized trial was conducted in 16 neonatal intensive care units among infants born at <30 weeks of gestation or with a birth weight of <1250 g who were ventilator-dependent in the second week after birth. Three centers performed MRI at term-equivalent age. Brain injury was assessed on MRI using the Kidokoro scoring system and compared between the 2 treatment groups. Both total and regional brain volumes were calculated using an automatic segmentation method and compared using multivariable regression analysis adjusted for baseline variables.

Results From the 3 centers, 78 infants participated in the study and 59 had acceptable MRI scans (hydrocortisone group, n = 31; placebo group, n = 28). Analyses of the median global brain abnormality score of the Kidokoro score showed no difference between the hydrocortisone and placebo groups (median, 7; IQR, 5-9 vs median, 8, IQR, 4-10, respectively; $P = .92$). In 39 infants, brain tissue volumes were measured, showing no differences in the adjusted mean total brain tissue volumes, at 352 ± 32 mL in the hydrocortisone group and 364 ± 51 mL in the placebo group ($P = .80$).

Conclusions Systemic hydrocortisone started in the second week after birth in ventilator-dependent infants born very preterm was not found to be associated with significant differences in brain development compared with placebo treatment. *(J Pediatr 2024;265:113807)*.

Trial Registration The SToP-BPD study was registered with the Netherlands Trial Register (NTR2768; registered on 17 February 2011; https://www.trialregister.nl/trial/2640) and the European Union Clinical Trials Register (EudraCT, 2010-023777-19; registered on 2 November 2010; https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-023777-19/NL).

Bronchopulmonary dysplasia (BPD) remains the most common complication of extremely preterm birth.[1] It is associated with increased risk for adverse long-term pulmonary and neurological outcomes.[2,3] Early postnatal dexamethasone improves short-term pulmonary function and significantly decreases the risk of BPD, but is associated with a higher risk of cerebral palsy and cognitive impairments later in life.[4,5] Observational studies using MRI techniques have suggested that the latter is caused by impaired cerebral cortical gray matter growth, and smaller total, and regional brain tissue volumes at term-equivalent age (TEA).[6,7] As a result of these adverse effects, clinicians are reluctant to use dexamethasone treatment in ventilator-dependent infants born preterm. An alternative corticosteroid, hydrocortisone, has been increasingly studied in the past decades for its efficacy, and short-term and long-term safety.

A small randomized placebo-controlled trial investigating a low dose of hydrocortisone (cumulative dose 17 mg/kg) after 1 week of age in ventilator-dependent infants born extremely preterm showed larger brain tissue volumes on MRI at TEA in the hydrocortisone group, and no differences on regional brain volumes between the hydrocortisone and placebo groups.[8] Retrospective observational trials investigating a higher dose of hydrocortisone initiated after 7 postnatal days demon-

BPD	Bronchopulmonary dysplasia
DWI	Diffusion-weighted imaging
PMA	Postmenstrual age
SToP-BPD	Systemic Hydrocortisone to Prevent Bronchopulmonary Dysplasia in Preterm Infants
SWI	Susceptibility-weighted imaging
TEA	Term-equivalent age
WM	White matter

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strated no differences in brain volumes at TEA compared with nontreated matched controls.[9,10] However, data from randomized controlled trials of brain growth after exposure to higher doses of hydrocortisone after the first week of life are lacking.

The Systemic Hydrocortisone to Prevent Bronchopulmonary Dysplasia in Preterm Infants (SToP-BPD) study investigated a high cumulative dose (72.5 mg/kg) of systemic hydrocortisone in ventilator-dependent infants born very preterm in the second week after birth. This large multicenter randomized placebo-controlled trial showed that hydrocortisone did not reduce the risk of the combined outcome death or BPD at 36 weeks' postmenstrual age (PMA), and that it was not associated with an increased risk for the combined outcome death or neurodevelopmental impairment at 2 years corrected age.[11,12] The predictive value of a neurodevelopmental assessment at 2 years of corrected age for long-term neurodevelopmental potential may be limited.[13] Advanced brain MRI techniques at TEA also can provide sensitive and objective information that is predictive of long-term outcomes.[14] Therefore, in this study, we evaluated whether a higher cumulative dose of systemic hydrocortisone initiated between 7 and 14 days after birth affects brain development assessed by MRI performed at TEA, compared with infants treated with placebo.

Methods

The SToP-BPD study, a multicenter randomized double-blind placebo-controlled trial, was performed between November 2011 and December 2016 (clinical trial registry: EudraCT, 2010-023777-19).[11,15,16] Infants with a gestational age of <30 weeks or with a birth weight of <1250 g who were ventilator dependent between 7 and 14 days after birth were randomly assigned to receive either hydrocortisone or placebo. Infants allocated to the intervention received systemic hydrocortisone course for 22 days with a cumulative dosage of 72.5 mg/kg. The use of open-label hydrocortisone during the trial was discouraged, but could be considered in infants with severe and progressive pulmonary deterioration or in infants who did not show an improvement in pulmonary condition after ≥10 days of trial medication.

The study protocol was approved by the human research ethics committees of the Academic Medical Center in Amsterdam, the Netherlands (reference number: 2010_297) and at each participating center.[11] Written informed consent was obtained from both parents before randomization.

MRI of the brain was not part of the original study protocol; however, in 3 participating centers, MRIs of the brain were routinely acquired around TEA in infants born very preterm as part of standard clinical care (University Medical Center Utrecht, University Hospital Brussel, and University Hospital Leuven). The 3 centers followed a predefined MRI protocol according to their institutional guidelines during the study period (**Supplement 1**). In all cases, the imaging protocol contained T1- and T2-weighted images, and in some cases, diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI). The available MRI images of study participants were collected for assessment of brain injury and volumetric measurements. Only high-quality images that were suitable for scoring and volumetric measurement were used. Quality of the scans was manually checked by the research team. Scans with severe motion artifacts or quality deficiencies that made biometric measures or volume calculations unreliable were excluded.

For assessment of brain injury, the scoring system described by Kidokoro et al. was used to evaluate cerebral white matter, cortical and deep gray matter, and cerebellar abnormalities.[17] Quantitative biometric values were measured by manually outlining the biparietal width, interhemispheric distance, lateral ventricular diameters, callosal thickness, deep gray matter area, and transcerebellar diameter using the medical image viewer 3D Slicer (www.slicer.org), and corrected for PMA age. A global brain abnormality score was calculated as the sum of the regional subscores and classified as normal if the total score was 0-3. Abnormalities were classified as mild (total score of 4-7), moderate (total score of 8-11), or severe (total score ≥12). All data were analyzed by a team of experts at the University Medical Center Utrecht masked for treatment allocation.

To quantify brain development at TEA, the axial or coronal T2-weighted images were segmented into different tissue classes using an automatic segmentation method as described by Makropoulos et al.[18] Regional brain volumes were measured on the basis of this anatomical segmentation procedure and segmented into 8 tissue classes: cerebrospinal fluid, cortical gray matter, white matter, ventricles, cerebellum, deep gray matter, brainstem, and hippocampi and amygdala. The sum of these tissue classes, except for cerebral spinal fluid, defined the total brain tissue volume. All segmented images from the 3 centers were manually reviewed for quality. Image stacks were excluded from further analysis if there were quality deficiencies that made segmentations and volume calculations unreliable. Owing to insufficient quality of the T2-weighted images, assessment of brain volumes was only possible for infants enrolled at the University Medical Center Utrecht.

Statistical Analysis

Baseline characteristics between the hydrocortisone and placebo group were summarized as mean ± SD, or as median (IQR), where appropriate. Clinical characteristics and neonatal morbidities of infants included in centers that used MRI as standard of care were compared with infants from centers without MRI. The clinical characteristics of infants with MRI and without MRI included in one of the 3 included centers were also compared. Data analysis was based on intention to treat, with all patients included in their randomly assigned treatment group regardless of protocol deviations or use of open-label hydrocortisone. The Kidokoro scores were compared between the 2 treatment groups

using the Mann-Whitney *U* test for nonparametric continuous variables and Fisher's exact test for categorical variables. Brain volumes were compared between the hydrocortisone and placebo groups using univariable linear regression analysis. Because birth weight, sex, and PMA at the time of scanning influence total brain tissue volumes, these variables were included in a multivariable linear regression model.[19-21] *Z*-scores for birth weight were computed according to the revised Fenton growth chart for infants born preterm.[22]

In the SToP-BPD study, a relatively high proportion of infants received open-label hydrocortisone during the study period. None of the participants in this cohort were treated with dexamethasone. To check the robustness of the results, we performed sensitivity analyses for the Kidokoro scores and the volumetric measurements by excluding infants who received any open-label corticosteroids during or after the study treatment course in the hydrocortisone and placebo groups.

For all treatment effect estimators, 95% CIs are presented; all analyses were performed using 2-sided tests and a *P* value of <.05 was regarded statistically significant. No adjustments for multiple comparisons were made. Data were analyzed using IBM SPSS 26.0 (IBM, Armonk, NY).

Results

Of the total SToP-BPD study cohort of 371 infants, 78 were born at centers performing standard MRI at TEA and 293 infants were born at other centers. At the 3 centers performing MRIs, 39 infants were allocated to the hydrocortisone group and 39 infants to the placebo group. Six infants died before TEA and 10 infants did not undergo MRI. Thus, a brain MRI at TEA was performed in 62 infants. Three MRIs were excluded because of severe motion artifacts and insufficient coronal image quality to perform biometric measures (**Figure**). For assessment of brain volumes, owing to insufficient quality of the images for the automatic segmentation method, MRIs from 15 infants from University Hospital Brussels and University Hospital Leuven were excluded as well as MRIs from 5 infants from

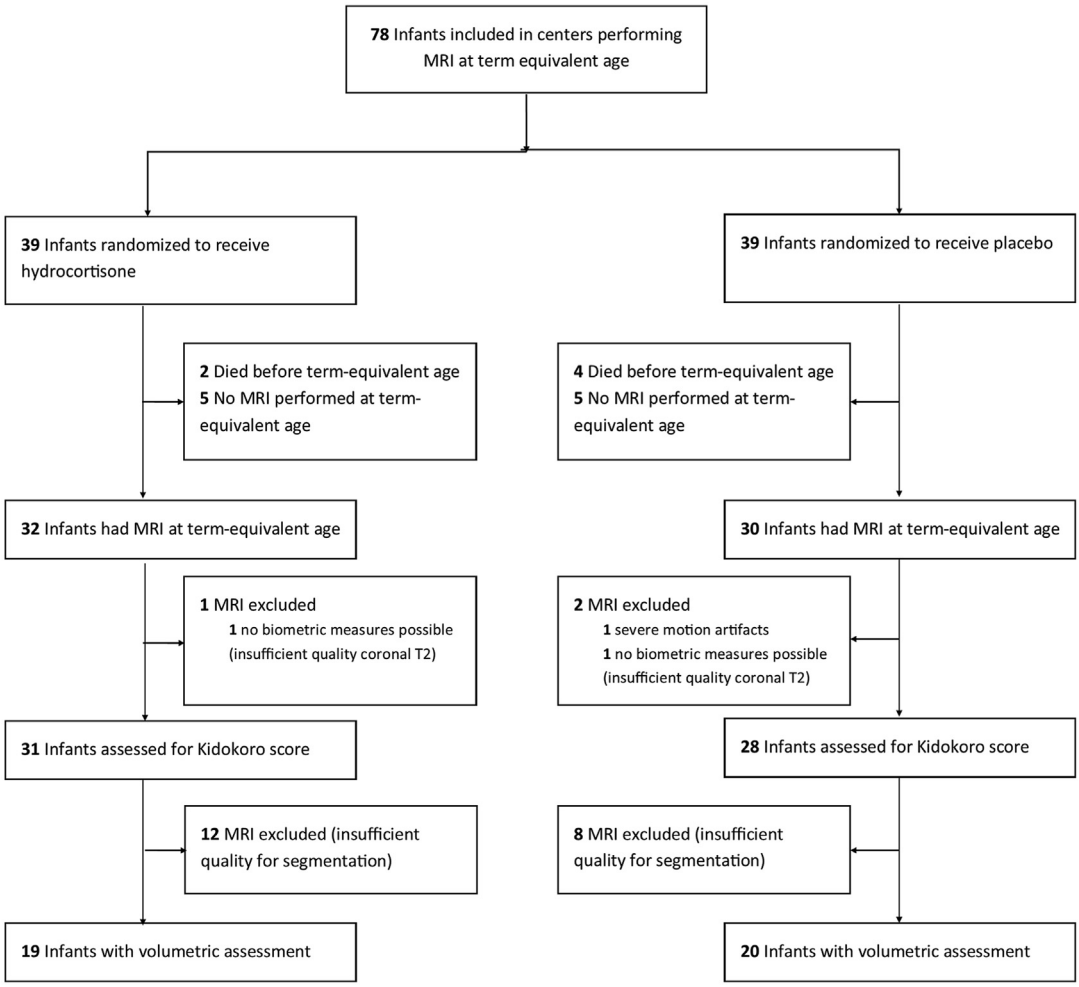

Figure. Trial flow diagram of infants included in 3 centers performing routine MRI at TEA.

the University Medical Center Utrecht. Brain volumes were calculated for 39 infants (19 in the hydrocortisone group and 20 in the placebo group, all from the University Medical Center Utrecht).

Table I, online (available at www.jpeds.com) compares the clinical characteristics from infants enrolled at the 3 MRI centers included in this study and the non-MRI centers. Infants from the 3 MRI centers had a lower mean airway pressure at randomization and fewer infections during hospitalization compared with infants enrolled at non-MRI centers. **Table II** compares clinical characteristics between the hydrocortisone and placebo groups for the 62 infants in this study with MRIs. More males were in the placebo group. Open-label use of hydrocortisone was used in both groups, but more often in the placebo group. **Table III**, online (available at www.jpeds.com) compares the clinical characteristics of 62 infants with MRI and 16 infants without MRI from the 3 MRI centers; no significant differences were identified.

The assessment of brain injury using the Kidokoro score was performed in 59 infants (hydrocortisone, n = 31; placebo, n = 20). To assess the Kidokoro score, T1- and T2-weighted images were available for all infants, DWI scans for 57 infants, and SWI scans for 38 infants. Analyses of the median global brain abnormality score of the Kidokoro score showed no difference between the hydrocortisone group and placebo group (median, 7 [IQR, 5-9] and median, 8 [IQR, 4-10], respectively; P = .92) (**Table IV**). No differences were observed comparing both treatment groups in terms of severity and subscores of the Kidokoro score (**Table IV**).

The adjusted mean total brain tissue volume was 352 ± 32 mL in the hydrocortisone treated infants and 364 ± 51 mL in the placebo group (P = .80) (**Table V**). Regional volumes of the cerebral white matter, cortical gray matter, deep gray matter, ventricles, hippocampi and amygdala, brainstem, and cerebellum were also comparable between the 2 treatment groups (**Table V**). Adjustment for PMA at time of scanning, z-score for birth weight, and sex did not change these findings (**Table V**).

Sensitivity analyses excluding infants who received any open-label hydrocortisone yielded similar results for the Kidokoro scores and brain volume measurements (**Tables VI** and **VII**, online (available at www.jpeds.com)).

Table II. Clinical characteristics of infants having MRI at TEA

Characteristics	Hydrocortisone (n = 32)	Placebo (n = 30)	*P* value
Infant birth characteristics			
Gestational age, weeks	25.8 (24.8-26.4)	25.9 (25.0-26.6)	.75
Birth weight, g	725 (603-864)	748 (648-888)	.53
Small for gestational age*	6 (18.8)	4 (13.3)	.73
Male	13 (40.6)	20 (66.7)	.047
Multiple birth	12 (37.5)	6 (20.0)	.17
Antenatal corticosteroids (any)	24 (75.0)	28 (93.3)	.08
Respiratory settings at randomization			
High frequency oscillatory ventilation	16 (50.0)	13 (43.3)	.62
Fraction of inspired oxygen	0.35 (0.29-0.45)	0.37 (0.33-0.45)	.36
Mean airway pressure	11.5 ± 2.2	11.3 ± 2.3	.62
Respiratory index†	4.2 (3.0-5.4)	3.9 (3.3-5.0)	.84
Other			
Infection‡	10 (31.3)	8 (26.7)	.78
Severe brain injury§	2 (6.3)	3 (10.0)	.67
Moderate/severe BPD at 36 weeks' PMA	19 (59.4)	14 (46.7)	.45
Neurodevelopmental impairment at 2 years corrected age¶	12 (41.4)	9 (31.0)	.59
Open-label use of hydrocortisone	8 (25.0)	17 (56.7)	.02
Estimated cumulative dose of hydrocortisone, mg/kg	72.5 (72.5-78.7)	65.5 (0.0-76.8)	.002
PMA at time of MRI scan, weeks	40.9 ± 0.6	41.3 ± 0.9	.17

Values are median (IQR), number (%), or mean ± SD.
*Small for gestational age was defined as birth weight less than the 10th percentile on the Fenton growth chart.
†Respiratory index was defined as mean airway pressure × fraction of inspired oxygen.
‡Includes infants with culture proven sepsis and necrotizing enterocolitis stage >2a according to Bell classification during admission at the neonatal intensive care unit.
§Includes infants with intraventricular hemorrhage grade >2, cystic periventricular leukomalacia and post hemorrhagic ventricular dilation during admission at the neonatal intensive care unit.
¶Neurodevelopmental impairment was defined as presence of ≥1 of cognitive and/or motor composite score I of <85 on the Bayley Scales of Infant and Toddler Development Third Edition, Dutch version; cerebral palsy >level II in the Gross Motor Function Classification System or hearing or visual impairment.

Discussion

In this study of ventilator-dependent infants born preterm, we evaluated the effect of hydrocortisone treatment vs placebo initiated between 7 and 14 days after birth on brain development at TEA using MRIs performed at 3 centers of the multicenter SToP-BPD study. We observed no significant differences between the treatment groups on the brain abnormalities assessed by the Kidokoro score and found similar brain volumes measured with an automatic segmentation method. These findings persisted after excluding infants who received any open-label hydrocortisone during and after the study period.

Two previous randomized placebo-controlled trials studied the effect of hydrocortisone on brain abnormalities and brain development.[8,23] The Effect of Early Low-dose Hydrocortisone on Survival Without Bronchopulmonary Dysplasia in Extremely Preterm Infants (PREMILOC) study found that hydrocortisone given shortly after birth to very infants born preterm was not associated with significant changes in white matter brain damage or overall moderate-to-severe brain lesions.[23] It is important to emphasize that hydrocortisone was administered prophylactically in the PREMILOC study, that is, independent of the risk of BPD or neurodevelopmental impairment. This practice is different from studies targeting a population at high risk for BPD (ventilator dependency after the first week of life) and thus at high risk for adverse neurodevelopmental outcomes later in life. Parikh et al investigated a low dose of hydrocortisone administered between 10 and 21 days of age in ventilator-dependent extremely low birth weight infants and reassuringly found no harmful effects on brain volumes at TEA compared with placebo.[8]

Table IV. Brain injury assessed by Kidokoro score between hydrocortisone and placebo group

Characteristics	Hydrocortisone (n = 31)	Placebo (n = 28)	*P* value
Global brain abnormality score	7 (5-9)	8 (4-10)	.92*
Kidokoro score severity			
Normal	2 (6.5)	3 (10.7)	.70†
Mild	17 (54.8)	11 (39.3)	
Moderate	9 (29.0)	10 (35.7)	
Severe	3 (9.7)	4 (14.3)	
Cerebral white matter subscore	4 (3-6)	4 (3-6)	.81*
Cystic lesions			
None	30 (96.8)	26 (92.9)	.46†
Focal unilateral	0 (0.0)	1 (3.6)	
Focal bilateral	0 (0.0)	0 (0.0)	
Extensive unilateral	1 (3.2)	0 (0.0)	
Extensive bilateral	0 (0.0)	1 (3.6)	
Focal signal abnormality			
None	24 (77.4)	21 (75.0)	.94†
Focal punctate	5 (16.1)	5 (17.9)	
Extensive punctate	1 (3.2)	2 (7.1)	
Linear	1 (3.2)	0 (0.0)	
Myelination delay			
PLIC and corona radiate	23 (74.2)	19 (67.9)	.66†
Only PLIC	8 (25.8)	8 (28.6)	
Minimal to no PLIC	0 (0.0)	1 (3.6)	
Thinning of the corpus callosum			
None	19 (61.3)	14 (50.0)	.59†
Partial	7 (22.6)	10 (35.7)	
Global	5 (16.1)	4 (14.3)	
Dilated lateral ventricles			
Both sides <7.5 mm	8 (25.8)	7 (25.0)	.24†
7.5 mm ≤ 1 side <10 mm	7 (22.6)	8 (28.6)	
7.5 mm ≤ both sides < 10 mm or 1 side ≥ 10 mm	14 (45.2)	7 (25.0)	
Both sides ≥ 10 mm	2 (6.5)	6 (21.4)	
Volume reduction			
cBPW ≥ 77 mm	2 (6.5)	2 (7.1)	.38†
77 mm > cBPW ≥ 72 mm	7 (22.6)	12 (42.9)	
72 mm > cBPW ≥ 67 mm	14 (45.2)	8 (28.6)	
67 mm < cBPW	8 (25.8)	6 (21.4)	
Cortical gray matter subscore	1 (0-3)	2 (0-3)	.34*
Signal abnormality			
None	31 (100.0)	28 (100.0)	1.00†
Focal unilateral	0 (0.0)	0 (0.0)	
Focal bilateral	0 (0.0)	0 (0.0)	
Extensive unilateral	0 (0.0)	0 (0.0)	
Extensive bilateral	0 (0.0)	0 (0.0)	
Gyral maturation			
Delay <2 weeks	20 (64.5)	16 (57.1)	.59†
2 weeks ≤ delay <4 weeks	10 (32.3)	12 (42.9)	
Delay ≥4 weeks	1 (3.2)	0 (0.0)	
Increased extracerebral space			
IHD <4 mm	13 (41.9)	9 (32.1)	.44†
4 mm ≤ IHD < 5 mm	7 (22.6)	7 (25.0)	
5 mm ≤ IHD < 6 mm	5 (16.1)	2 (7.1)	
IHD ≥ 6 mm	6 (19.4)	10 (35.7)	
Deep gray matter subscore	0 (0-0)	0 (0-1)	.89*
Signal abnormality			
None	30 (96.8)	28 (100.0)	1.00†
Focal unilateral	0 (0.0)	0 (0.0)	
Focal bilateral	0 (0.0)	0 (0.0)	
Extensive unilateral	1 (3.2)	0 (0.0)	
Extensive bilateral	0 (0.0)	0 (0.0)	
Volume reduction			
cDGMA ≥ 9.5 cm^2	24 (77.4)	21 (75.0)	.93†
9.5 cm^2 > cDGMA ≥ 8.5 cm^2	6 (19.4)	6 (21.4)	
8.5 cm^2 > cDGMA ≥ 7.5 cm^2	1 (3.2)	0 (0.0)	
7.5 cm^2 < cDGMA	0 (0.0)	1 (3.6)	
Cerebellum subscore	1 (0-2)	1 (0-1)	.73*
Signal abnormality			
None	22 (71.0)	18 (64.3)	.84†
Punctate unilateral	5 (16.1)	7 (25.0)	
Punctate bilateral	3 (9.7)	2 (7.1)	
Extensive unilateral	1 (3.2)	1 (3.6)	
Extensive bilateral	0 (0.0)	0 (0.0)	
Volume reduction			
cTCD ≥ 50 mm	21 (67.7)	18 (64.3)	.36†
50 mm > cTCD ≥ 47 mm	4 (12.9)	8 (28.6)	
47 mm > cTCD ≥ 44 mm	3 (9.7)	1 (3.6)	
44 mm < cTCD	3 (9.7)	1 (3.6)	

cBPW, biparietal width corrected for PMA; *cDGMA*, deep gray matter corrected for PMA; *cTCD*, transcerebellar diameter corrected for PMA; *IHD*, interhemispheric distance; *PLIC*, posterior limb of internal capsule.
Values are median (IQR) or number (%).
*Mann-Whitney *U* test.
†Fisher's exact test.

Another important characteristic from the PREMILOC study is the low dose of hydrocortisone used, which may have attenuated possible adverse effects of hydrocortisone on the brain. The possible impact of cumulative dose on brain development was initially addressed by retrospective observational trials investigating a higher dose of hydrocortisone initiated after 7 days of postnatal life for BPD in ventilator-dependent very infants born preterm, which demonstrated no differences in brain volumes at TEA using quantitative volumetric MRI techniques compared with non-treated matched controls.[9,10] The SToP-BPD study used a randomized design and a similar cumulative dose (72.5 mg/kg) and our study confirms these findings. Together with a similar rate of death or neurodevelopmental impairment at 2 years corrected age between the hydrocortisone and placebo group,[12,24] these findings strengthen the evidence that hydrocortisone does not affect brain development, even in higher doses, and administered at later postnatal ages.

A systematic review and meta-analysis by Romberg et al aimed to identify reference ranges for cerebral and cerebellar volumes in very preterm and very low birth weight infants at TEA showed a mean total brain volume of 379 ± 72 mL and a mean total cerebellar volume of 21 ± 6 mL.[25] In our study, we found slightly lower total brain tissue volumes in both groups, and similar cerebellar volumes compared with this reference population. Despite this possibly negligible decrease in total brain volume, the mean differences between both groups in total brain tissue volume and cerebellar volume were small (1%-3% lower in the hydrocortisone group) and not significantly different.

In contrast with hydrocortisone, Parikh et al showed that dexamethasone treatment (with a mean cumulative dose of 2.8 mg/kg) reduced total cerebral tissue volume by 10% and cerebellar volume by 20%.[7] Decreased brain tissue volumes at TEA in infants born preterm are associated with impaired neurocognitive outcomes later in life.[26] This difference on brain development between dexamethasone and hydrocortisone might be explained by a difference in receptor

Table V. Brain volumes for the different tissue classes between hydrocortisone and placebo group

Characteristics	Hydrocortisone (n = 19)	Placebo (n = 20)	Crude mean difference (95% CI)	Adjusted mean difference (95% CI)*	*P* value†
Total brain tissue volume, mL‡	352 (32)	364 (51)	−12.1 (−40.0 to 15.9)	−3.1 (−27.6 to 21.3)	.80
White matter, mL	143 (12)	147 (19)	−4.2 (−14.7 to 6.2)	−1.8 (−11.3 to 7.6)	.69
Cortical gray matter, mL	141 (15)	148 (24)	−7.0 (−20.3 to 6.2)	−2.4 (−14.3 to 9.4)	.68
Deep gray matter, mL	25 (3)	26 (3)	−0.3 (−2.0 to 1.5)	0.2 (−1.3 to 1.7)	.78
Ventricles, mL	10 (5)	9 (3)	0.4 (−2.3 to 3.1)	0.7 (−2.1 to 3.4)	.62
Hippocampi and amygdala, mL	2 (0.2)	2 (0.3)	−0.1 (−0.2 to 0.1)	−0.02 (−0.17 to 0.14)	.82
Brainstem, mL	6 (1)	6 (1)	0.03 (−0.4 to 0.5)	0.1 (−0.2 to 0.5)	.47
Cerebellum, mL	25 (5)	26 (5)	−0.9 (−4.0 to 2.2)	0.1 (−2.7 to 3.0)	.92

*Mean difference adjusted for PMA at scan, z-score birth weight, and sex using a linear regression model.
†Adjusted *P* value.
‡Total brain tissue volume is defined as the sum of white matter, cortical gray matter, deep gray matter, ventricles, hippocampi and amygdala, brainstem, and cerebellum.

activation. Experimental studies have shown that corticosteroids enter the brain via simple diffusion across the blood-brain barrier.[27,28] In the brain, corticosteroids act on the intracellular glucocorticoid and mineralocorticoid receptors. Dexamethasone primarily binds to glucocorticoid receptors, whereas hydrocortisone preferentially binds mineralocorticoid receptors. Previous studies of corticosteroids exposure in animals have shown that the activation of the glucocorticoid receptor leads to adverse neuronal effects.[29,30] The fact that hydrocortisone binds mineralocorticoid receptors may explain, at least in part, the less harmful effects of hydrocortisone treatment on the preterm developing brain.

Evaluation of the effect of postnatal corticosteroids on brain development is important because the administration of these treatments during the neonatal period could produce different effects on brain structures and development, depending on timing and doses. A recent scoping review by Robles et al identifying literature on the effects of glucocorticoids on brain structural development in infants born preterm shows that there is considerable interest in this topic among researchers and clinicians.[31] However, relatively few studies in humans have directly assessed the effect of corticosteroids on brain structural development using advanced imaging modalities.[31] For this substudy of the SToP-BPD study, we used sophisticated MRI metrics and an unbiased scoring system to evaluate brain injury on MRI.[17] Additionally, we used an automatic segmentation technique to accurately quantify both total and regional brain volumes.[18] Evaluation of the effect of postnatal corticosteroids on the brain at later ages is also important, because the effects may not be evident until the brain structure is more mature. Hence, follow-up of the SToP-BPD study cohort at 5 years of corrected age, including neurodevelopmental assessment, is currently under way.

Our study has some limitations that need to be addressed. First, only 3 centers participating in the SToP-BPD study routinely performed MRI at TEA in these patients, leading to a relatively small number of infants included in this substudy. Infants were equally distributed across the hydrocortisone and placebo groups, but differences in some clinical characteristics were found. Reassuringly, our multivariable regression models adjusted for PMA, birth weight *z*-score, and sex yielded similar results. Second, a relatively high proportion of infants received open-label hydrocortisone, especially those infants allocated to the placebo group. This factor may have masked a possible adverse effect of hydrocortisone on brain development. However, excluding these infants from our analysis for brain injury and brain volumes did not change the results of the study. Third, the MRI protocols were not the same across centers, resulting in varying image qualities and availability of DWI and SWI scans. The lack of a SWI and/or DWI can potentially make the Kidokoro score less reliable. Furthermore, automatic segmentation for volumetric analysis is challenging and is only possible in high-quality MRI images. Owing to the differences in MRI protocols, only the 39 infants from the University Medical Center Utrecht were included in the volumetric analysis, causing potential selection bias and making the results less generalizable for the global preterm population. Finally, the SToP-BPD trial was only powered for the primary outcome. Although we found no differences in brain development, this analysis should be regarded as exploratory and hypothesis generating only. Future studies on postnatal corticosteroids should be adequately powered to detect differences in brain development, to validate our observations.

In conclusion, systemic hydrocortisone started in the second week of postnatal life in ventilator-dependent infants very born preterm did not seem to be associated with significant differences in brain development compared with placebo as assessed by MRI. Evaluation of the effect of postnatal corticosteroids on brain development in infancy and later childhood should be included in larger future trials to help researchers and clinicians better understand the effects of this treatment on neurodevelopment. ■

Declaration of Competing Interest

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full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data Statement

Data sharing statement available at "www.jpeds.com".

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